FDA Cardiologist's Perspective on RECORD

Joint Meeting of the Endocrinologic and Metabolic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee
Avandia® (rosiglitazone) – July 13-14, 2010

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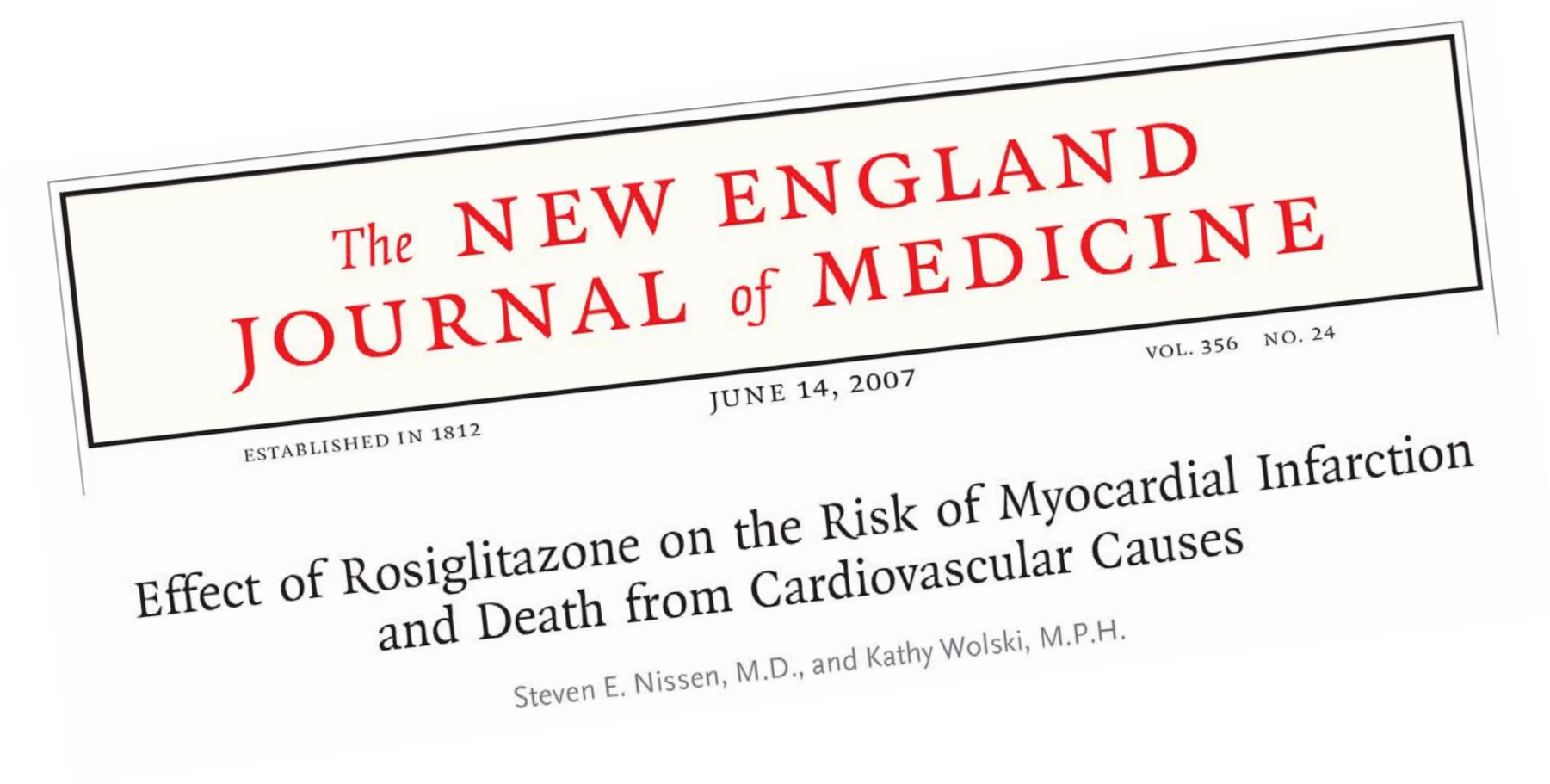
Outline of Presentation

- Why are we here?
- RECORD: Key features
- RECORD: Ascertainment bias
- Conclusions

Why are we here?

Nissen/Wolski Meta-analysis



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Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

Nissen/Wolski Meta-analysis

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

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Limitations on Meta-analysis (1)

- Trials not originally intended to explore CV outcomes.
- No patient-level source data.
- Results were based on a relatively small number of events; small changes in classification of events would alter odds ratios.
- Most trials did not centrally adjudicate CV outcomes.

Limitations on Meta-analysis (2)

- Definitions of MI were not available.
- Many trials were small and short-term, with few adverse CV events or deaths.
- From editorial of Psaty and Furberg: "*In their discussion, the authors properly emphasize the fragility of their findings*."
- A meta-analysis is always considered less convincing than a large prospective trial designed to assess the outcome of interest.

Nissen/Wolski Meta-analysis: Conclusions

- Statistically significant finding on myocardial infarction (p=0.03) – many limitations, would need confirmation
- Non-statistically significant finding on cardiovascular mortality – also many limitations – but finding seems concerning (death)
- No assessment of major adverse cardiovascular events (MACE), stroke

RECORD:
New large, randomized, controlled, clinical trial - conducted by GlaxoSmithKline

RECORD: Key Features

- Aim was to show non-inferiority of combination therapy with rosiglitazone to therapy without rosiglitazone with respect to CV outcomes.
- Open-label trial – key limitation
- Primary endpoint: time-to-first cardiovascular hospitalization or cardiovascular death
- Adjudication of potential endpoint events by a Clinical Endpoint Committee (CEC), blinded to treatment assignment, but…
- Potential for ascertainment bias

Ascertainment Bias (1):

- Protocol directed that "all potential CV hospitalization…and CV death endpoints will be reported…in the CRF."
- Reporting (or non-reporting) of potential endpoint events was at the discretion of the clinical investigator.
- Investigator was, of course, aware of treatment assignment.

Ascertainment Bias (2):

- Adverse events not considered "potential" endpoint events in investigator's opinion would not be reported to the CEC.
- CEC's primary charge was to "downgrade" events that the investigator deemed to be potential endpoints – to overrule her/him.
- By design, there was limited provision to search for events that investigators deemed not to be endpoint events and permit the CEC to "upgrade" them.

Ascertainment Bias (3):

- Example:
  - Consider a patient hospitalized with pneumonia and “a touch of CHF.” Clinical investigator judged whether this was a “potential endpoint event,” i.e., a cardiovascular hospitalization.
- If operational, ascertainment bias could have affected all endpoints, with the probable exception of all-cause mortality.

Cast a Wide Net?

- Protocol could have set a low threshold for referral of adverse events for blinded adjudication, to help ensure that all endpoint events were captured, but…
- This was not how RECORD was designed/conducted.

Eight Adverse Events Not Adjudicated*

- MI reported; then deleted
- Hospitalization for pulmonary edema
- Hospitalization for intracerebral hematoma
- Hospitalization for CHF
- Hospitalization for MI
- Hospitalization for collapse; atrial fibrillation
- Hospitalization for amputation and peripheral arterial disease
- Hosp. for facial paralysis with CT scan

*** From review of Thomas Marciniak; page 95**

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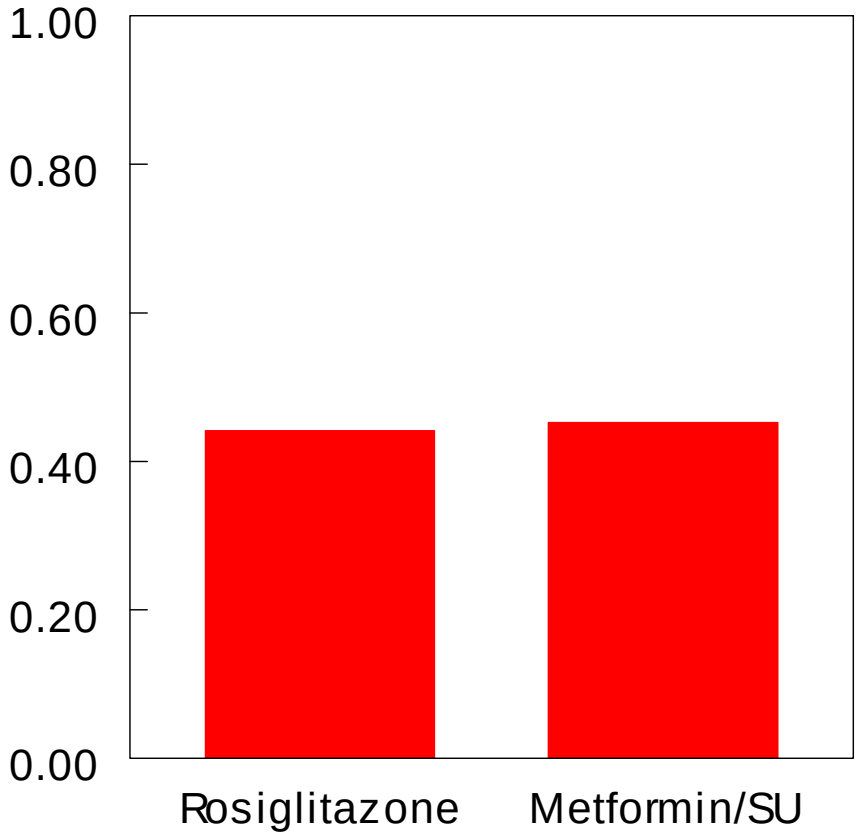
*** All 8 were in the rosiglitazone group**

Some Reassurance Against Bias

- Fractions of total deaths deemed by the CEC to be CV in nature (i.e., endpoint events) were virtually the same in both treatment groups (~45%).



Is There Unequivocal Evidence of Ascertainment Bias?

- No, but cannot rule it out.
- Could one find "unadjudicated" events in the control arm? Possibly.
- To verify an extreme ascertainment bias as suggested in Dr. Marciniak's review (8:0), one would need to examine CRFs for all subjects:
  - Pre-specified plan
  - Systematic, blinded analysis of case report forms
  - Labor intensive

RECORD: Interpretation of Findings

- With open-label design, the possibility of ascertainment bias confounds interpretation of the primary endpoint, as well as major adverse cardiovascular events (MACE: cardiovascular death, MI, stroke).

Major Adverse Cardiovascular Events (MACE) in RECORD

- Results of analyses performed by GSK:

Hazard ratio = 0.91 (95% C.I. 0.73 to 1.13)

- Dr. Marciniak's independent results:

Hazard Ratio = 1.07 (95% C.I. 0.86 to 1.33)

- Sponsor's calculated upper bound of the 95% C.I. is <1.3
- Dr. Marciniak's upper bound slightly exceeds 1.3

Acute MI in RECORD: GSK Findings

Rosiglitazone	64/2220 (2.9%)
Control	56/2227 (2.5%)

HR 1.14, 95% C.I.: 0.80 to 1.63; p=0.47

Acute MI in RECORD: Findings of Division of Cardiovascular and Renal Products

Dr. T. Marciniak:

- Worked independently
- Applied modified criteria for acute MI, post hoc
- Included probable MIs without positive biomarkers
- Net addition of 19 MIs to the rosiglitazone group and 3 to the control group

Results: HR 1.38, 95% C.I.: 0.99 to 1.93; p=NS

Acute MI in RECORD

- Unfavorable trend for MIs in RECORD (GSK: slight trend; Dr. Marciniak: strong trend)
- Results were not statistically significant for either the GSK analysis or for Dr. Marciniak's post hoc re-adjudication and analysis.
- Findings on MI seem inconclusive
- Viewed in isolation, the results are not particularly reassuring; however,
- Findings on MI do not substantiate hypothesis in the Nissen/Wolski meta-analysis on excess MIs.

Re-adjudication of MIs in RECORD?

There may be some merit in re-adjudicating MIs in RECORD; however, re-analysis would need to be rigorous:

- Diagnostic criteria considered and agreed upon by experts in advance
- Adjudication by a committee
- Use of rigorous blinding

RECORD: All-Cause Mortality

- All-cause mortality is a “hard” endpoint
- Objective
- Insensitive to bias
- Little need for adjudication
- Verifiable, using public records, and…
- Germane because of the findings in the Nissen/Wolski meta-analysis

All-Cause Mortality: 2 GSK Analyses

- **During CV follow-up:** from the time of premature discontinuation of study medication until study end, complete withdrawal or move to “survival status” updates only, whichever was sooner.
- **Including “survival status updates:”** subjects who refused consent for protocol procedures, but consented to be followed for survival status.

All-Cause Mortality: 2 GSK Analyses

- **During CV follow-up:**

  Rosiglitazone 111/2220 (5.0%)

  Control 139/2227 (6.2%)

  HR 0.79, 95% CI: 0.62, 1.02; p=0.07

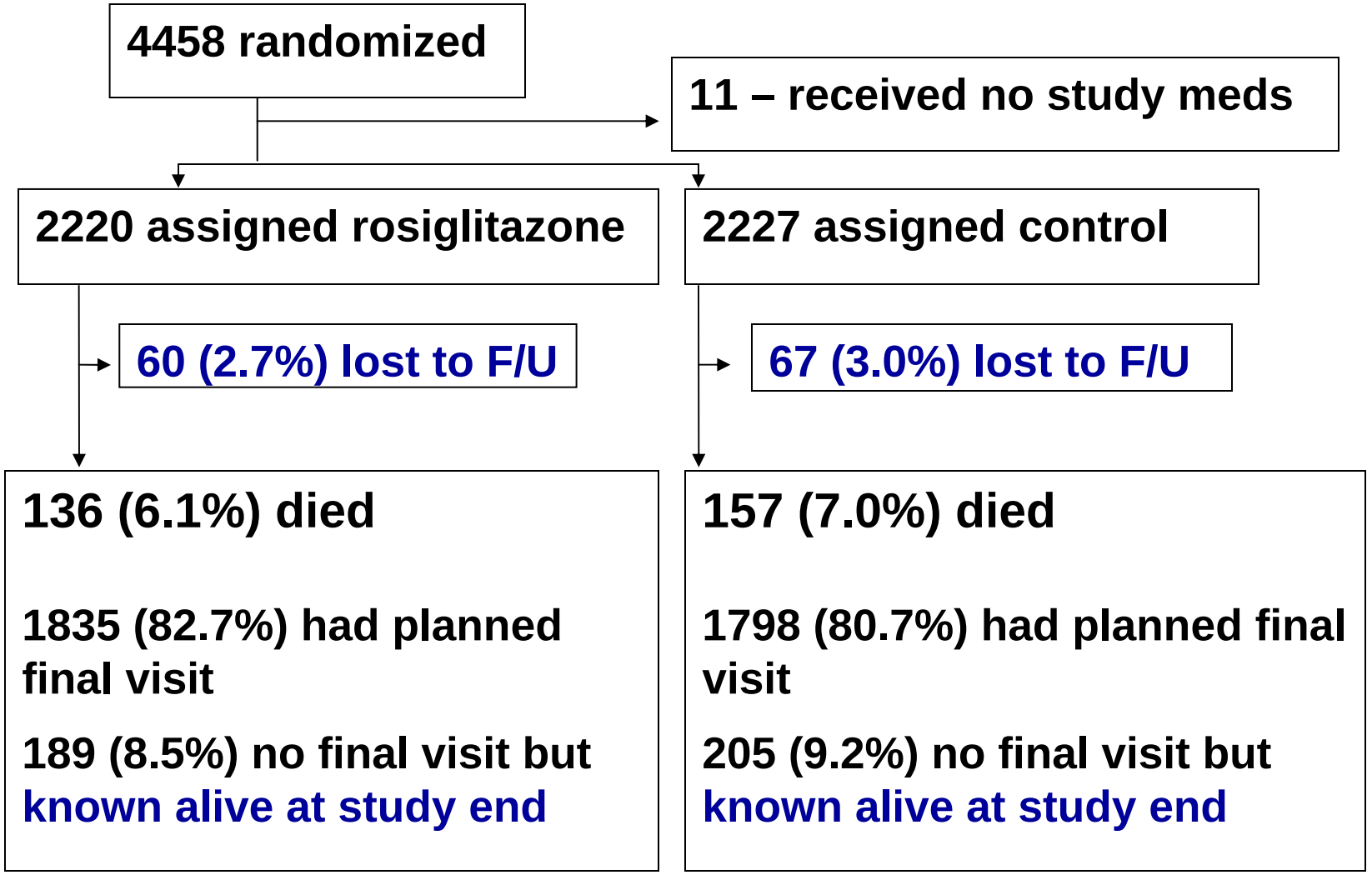
- **Including survival status updates:**

  Rosiglitazone 136/2220 (6.1%)

  Control 157/2227 (7.0%)

  HR 0.86, 95% CI: 0.68, 1.08; p=0.19

All-Cause Mortality: Certainty of Follow-up



All-Cause Mortality: Randomized Treatment Phase Plus 30 Days

- **Including survival status updates:**

  Rosiglitazone 136/2220 (6.1%)

  Control 157/2227 (7.0%)

  HR 0.86, 95% CI: 0.68, 1.08; p=0.19

All-Cause Mortality: Conclusions (1)

- All-cause mortality was probably the most interpretable endpoint evaluated in RECORD.
- GSK analysis is very reassuring: favorable trend for rosiglitazone on all-cause mortality.
- Some uncertainty because of subjects lost to follow-up; subjects with errors in censoring date.
- Errors in censoring date have minimal effect on results.
- Errors in vital status are critical, but veracity could be checked for subjects where there is uncertainty.

All-Cause Mortality: Conclusions (2)

- Analysis of randomized treatment phase plus 30 days is highly interpretable, largely eliminates concern regarding missing data.
- Results are very reassuring.
- Key Point: If the almost statistically significant excess in death from CV causes reported in the Nissen/Wolski meta-analysis is viewed as a hypothesis for future study, that hypothesis is not substantiated by the results of RECORD.

Conclusions on RECORD (1)

- For regulatory purposes, RECORD is viewed as a means to test two hypotheses generated by the meta-analysis of Nissen and Wolski:
  1. Rosiglitazone increases the risk of MI
  2. Rosiglitazone increases the risk of cardiovascular mortality

Conclusions on RECORD (2)

- There are some questions on the validity of the MI results because of possible ascertainment bias, but no analysis of RECORD has shown a statistically significant increase in MIs.
- GSK's results on cardiovascular mortality favor rosiglitazone, but interpretation is in question because of possible ascertainment bias.
- Results for all-cause mortality are largely free of bias, and are reassuring.

Conclusions on RECORD (3)

- RECORD's results are not as definitive as they might have been, because of:
  - a key design issue (not "casting a wide net" to ascertain endpoint events)
  - possible ascertainment bias by investigators
  - questions regarding mortality follow-up.
- Nevertheless, the results of RECORD do not substantiate the findings from the Nissen/Wolski meta-analysis on myocardial infarction and cardiovascular death.

- Thank you for your attention!